REMARKS

The paper is in response to the Office Action mailed June 23, 2010 ("the Office Action"). Claims 1, 2, 7, and 14 are currently amended and are now pending in view of the amendments. All other claims have been cancelled. Applicants respectfully request reconsideration of the application in view of the above amendments to the claims and the following remarks. For Examiner's convenience and reference, Applicants present remarks in the order that the Office Action raises the corresponding issues.

In connection with the prosecution of this case and any related cases, Applicants have, and/or may, discuss various aspects of the disclosure of the cited references as those references are then understood by the Applicants. Because such discussion could reflect an incomplete or incorrect understanding of one or more of the references, the position of the Applicants with respect to a reference is not necessarily fixed or irrevocable. Applicants thus hereby reserve the right, both during and after prosecution of this case, to modify the views expressed with regard to any reference.

Please note that Applicants do not intend the following remarks to be an exhaustive enumeration of the distinctions between any cited references and the claims. Rather, Applicants present the distinctions below solely by way of example to illustrate some of the differences between the claims and the cited references. Finally, Applicants request that Examiner carefully review any references discussed below to ensure that Applicants' understanding and discussion of any reference is consistent with Examiner's understanding.

Unless otherwise explicitly stated, the term "Applicants" is used herein generically and may refer to a single inventor, a set of inventors, an appropriate assignee, or any other entity or person with authority to prosecute this application.

Claim Objections

The Office Action objects to claims 1, 2, 4-18 for various reasons. In response, Applicant has cancelled all but claims 1-2, 7, and 14, and amended claims 1-2, 7, and 14. As such, the objections should be overcome in view of the amendment to the claims.

Rejection Under 35 U.S.C. §112, ¶2

The Office Action rejects claims 9 and 11-13 under 35 U.S.C. §112, ¶2. Applicant has cancelled these claims, and thereby this rejection is moot.

Rejection under 35 U.S.C §103(a)

The Office action rejects claims 1, 2, and 4-18 under 35 U.S.C §103(a) over Schlag et al. (U.S. Patent No.6,358,918) in view of Tsikas et al. (*Biochem. Biophys. Acta* (2001) 1546, 422-434) and Hallström et al. (*Circulation* (2002) 105, 3032-3038). Applicant respectfully asserts that the presently pending claims are patentable over this combination of references for at least the following reasons.

35 U.S.C §103(a), "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." According to MPEP §2142, "[t]he examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness." Finally, MPEP 2141.III notes that:

> "The key to supporting any rejection under 35 U.S.C. 103 is the ***clear articulation of the reason(s) why the claimed invention would have been obvious.*** The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'***[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.***'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396." (emphasis added)

Under the guidelines in the MPEP, Examiner must establish that the references teach or suggest each and every claim element or explain "why the difference(s) between the prior art and the claimed invention would have been obvious".[1] The Office Action does neither.

In accordance with Applicant's understanding, Schlag relates to a preparation comprising thiol-group-containing proteins which are heat-treated, dissolved, and which are characterized in that they are processed for improving the perfusion and microcirculation in patients (column 2 lines 36 to 42 and claim 1). In such preparation according to Schlag, at least 40% of the thiol groups are capable of being nitrosated. In particular, Schlag relates to a pharmaceutical preparation which basically may contain any **protein** with a "free" thiol group, yet for the purposes of the present invention therapeutically usable **proteins** are preferred, physiological **proteins** or human **proteins** derived from blood" (emphasis added.) Also, the proteins according to Schlag (claim 1) have molecular weights in the range of ca. 35,000 g/mol (plasminogen activator) up to ca. 340,000 g/mol (fibrinogen).

In column 2, lines 61 and 62 to which the Office Action refers, it is not at all indicated that the composition may comprise a low-molecular weight protein. In contrast to that it is said: "According to the present invention, high-molecular proteins are preferred over low-molecular proteins, such as, e.g., glutathione" (column 2, lines 61 and 62). It is submitted that glutathione would be not regarded as a protein as used by Schlag because the proteins indicated to be useful by Schlag have molecular weights in the range of ca. 35,000 g/mol up to ca. 340,000 g/mol, whereas glutathione in fact is a tripeptide with a molecular weight of 305 g/mol which even does not show the normal peptide binding because the amide bond between glutaminic acid and cystein is formed via the γ-carboxyl group of the glutaminic acid and not via the α-c arboxylic group as would be the case in a true peptide.

In view of the foregoing, it is therefore submitted that for a skilled person in the relevant art glutathione is to be regarded as excluded and not at all as included into the invention of Schlag from the description, and it is not obvious to combine a protein of Schlag with a low

[1] MPEP §2143.03 ("'All words in a claim must be considered in judging the patentability of that claim against the prior art.' In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)."
MPEP §2141.III ("The prior art reference (or references when combined) need not teach or suggest all the claim limitations, however, ***Office personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art***." emphasis added).

molecular weight compound comprising thiol groups with a molecular weight of 10,000 g/mol or less because Schlag specifically and expressly indicates that such a low molecular compound is NOT preferred, beside the fact that glutathione is not a true protein. The only combination which could be derived from Schlag is a mixture of any of the proteins listed in claim 1 of Schlag which proteins being selected from the group consisting of albumin, orosomucoid, tissue-plasminogen activator, fibrinogen, Lys-plasminogen, and hemoglobin.

Furthermore, in column 1, lines 48 to 58 of Schlag there is disclosed: "This level also matches the known fact that in preparations of proteins having potentially free thiol groups, only 20 to 35% are, in fact, present in free, reduced SH form. Particularly in protein preparations derived from blood or which are contacted with plasma or plasma derivatives in the course of their preparation procedure, the remaining 65 to 80% are blocked, mostly by mixed S-S bonds with small, thiol carrying compounds, e.g. free L-cysteine or **glutathione**, respectively (Katachalski et al., J. Am. Chem. Soc. 79 (1957), 4096-4099, DeMaster et al., Biochemistry 34 (1995), 11494-11499)." From that a skilled person in the art rather would expect that small, thiolcarrying compounds, e.g. free L-cysteine or **glutathione**, respectively are not desired but should be avoided because of blocking the free –SH groups of protein.

In sum, it is submitted that a skilled person in no way would be motivated from Schlag to use a low molecular weight compound comprising thiol groups with a molecular weight of 10,000 g/mol and less and, reconsideration is respectfully requested.

In the scientific paper of Tsikas, it is alleged that the single SH group of albumin possibly could be S-transnitrosated by the compounds S-nitrosocysteine and S-nitrosoglutathione. Any combination, however it not indicated or suggested in Tsikas. Also, despite of the explanation in the Office Action, it is not understood from Tsikas why a skilled person would be motivated from Tsikas (in combination with other references) to use a combination of S-nitroso albumin and S-nitroso glutathione. Namely, if already S-nitroso albumin is used, for what reason should one use in addition any further S-nitrosated compounds which are prone, according to Tsikas to transnitrosate a protein which is S-nitrosated already? Applicant respectfully submits that one of skill in the art would have no reason for combining such compounds.

However, the aforementioned teachings of Tsikas are not relevant for the presently claimed invention because according to the present invention no nitrosated low molecular compound such as S-nitroso glutathione is used, but the low molecular compound having a molecular weight of 10,000 g/mol, or less comprises thiol groups which are sulfhydryl groups (-SH) and/or disulfide groups (-S-S-), as indicated on page 3, paragraph 3 of the present application, furthermore a detailed compound list may be found in the penultimate paragraph on page 3. In fact, present claim 1 recites "a compound containing thiol groups and having a molecular weight of 10,000 g/mol and less, which compound is reduced glutathione."

It is therefore submitted that Tsikas in combination with Schlag and Hallström, does not result in the present invention; because even when ignoring the fact that hindsight was used to make the combination of references, which is generated by picking together possible pieces of the present invention from several pieces of literature, a combination of S-nitrosated protein with S-nitrosated low molecular compound is not subject of the present invention and thus cannot make obvious the present invention.

In the scientific paper of Hallström, it is indicated that long lasting release of NO by S-NO-HSA (S-nitrosated human serum albumin) provides significant protection of skeletal muscle from Ischemia/Reperfusion injury. Under the "Discussion" on page 3036, it is indicated that the data provided show that S-NO-HSA preserves the function of eNOS, stabilizes the basal production of NO, decreases production of oxidized species, and therefore has beneficial effects. Nothing else is disclosed in Hallström, particularly no combination of S-NO-HSA with any other compound is indicated or suggested.

In view of the foregoing, Applicant respectfully asserts that the combination of references does not teach or suggest each and every element of the currently pending claims. The combination does not or suggest a therapy for ischemia that includes administering a composition having "a therapeutic protein having SH-groups which are nitrosated, which therapeutic protein is S-nitroso albumin; and a compound containing thiol groups and having a molecular weight of 10,000 g/mol and less, which compound is reduced glutathione," as recited in claim 1. None of the reference, along or in combination, teaches or suggests a composition having the recited components for use in therapy for ischemia. Moreover, none of the references

teach or suggest that a glutathione containing thiol groups and having a molecular weight of 10,000 g/mol and less can be useful for treating ischemia. Please note, that a S-nitroso glutathione is not claimed. In sum, in none of the references there is indicated to use a combination, with the exception of a mixture of any of the proteins listed in claim 1 of Schlag, which proteins being selected from the group consisting of albumin, orosomucoid, tissue-plasminogen activator, fibrinogen, Lys-plasminogen, hemoglobin; which mixture, however, is not the subject of the present invention.

Applicant respectfully asserts that only impermissible hindsight as been used to make the combination of references. This combination of references could only be made after first reviewing the Applicant's application and using the claims as a roadmap.

Applicant also respectfully submits that the presently claimed invention yields surprising and unexpected results. It is submitted that the presently invention shows unexpected results despite the allegations in the Office action. Since none of the references cited, e.g. in any combination, it could be expected that a combination of the nitrosated protein with a thiol comprising low molecular compound according to the present invention would show better activity than the nitrosated protein alone. As such, the unexpected results are shown in the examples of the present application, which shows the composition as claimed is superior and has surprising and unexpected results.

In view of the foregoing, a *prima facie* case of obviousness has not been established for the presently pending claims. Therefore, Applicant respectfully requests withdrawal of the rejection and allowance of the presently pending claims.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that the other rejections to the claims are now moot and do not, therefore, need to be addressed individually at this time. It will be appreciated, however, that this should not be construed as Applicant acquiescing to any of the purported teachings or assertions made in the last action regarding the cited art or the pending application, including any official notice. Instead, Applicant reserves the right to challenge any of the purported teachings or assertions made in the last action at any appropriate time in the

future, should the need arise. Furthermore, to the extent that the Examiner has relied on any Official Notice, explicitly or implicitly, Applicant specifically requests that the Examiner provide references supporting the teachings officially noticed, as well as provide the required motivation or suggestion to combine references with the other art of record.

For at least the foregoing reasons, Applicant respectfully submits that the pending claims are neither anticipated by nor made obvious by the art of record. In the event that the Examiner finds any remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview, the Examiner is requested to contact the undersigned attorney.

Dated this 30th day of September, 2010.

Respectfully submitted,

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